DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20852

Date: February 13, 2009

Meeting ID: CRMTS 6919
Application type and number: BLA STN 125197/0
Product name: Sipuleucel-T
Sponsor: Dendreon Corporation
Meeting type: B
Meeting category: Type C, CMC discussion
Meeting date & time: January 15, 2009, 2:30-3:30 pm
Meeting format: teleconference
Meeting Chair/Recorder: Lori Tull, RAC

Attendees

Sponsor Representatives

Elizabeth Smith, Regulatory Affairs
Mark Johnson, Engineering
Ernie Bognar, Plant Manager
Mike Covington, QA
Mary Coon, Quality
Cyril Possa, Validation
Georgeta Puscalau, QC
Tim Wood, QC
Connie Spooner, Regulatory Affairs

FDA
Keith Wonnacott, PhD, Chief, Cell Therapies Branch, Division of Cell and Gene Therapies
Thomas Finn, PhD, Product Reviewer, Gene Therapies Branch, Division of Cell and Gene Therapies
Gang Wang, PhD, Reviewer, Division of Manufacturing and Product Quality
Raj Puri, MD, PhD, Director, Division of Cell and Gene Therapies
Lori Tull, RAC, Regulatory Project Manager, Office of Cellular, Tissue, and Gene Therapies

Background and Objectives

This meeting was requested by the sponsor on November 19, 2008 to discuss Dendreon's conceptual design of the planned expansion to the manufacturing capacity of the Sipuleucel-T manufacturing plant (Morris Plains, NJ). The information package was submitted on December 11, 2008.

Discussion
Facility Expansion

1. The facility expansion [redacted] design that includes corridors and (b)(4) of production modules, each with [redacted] workstations, incubator room and gown-in and gown-out areas), allowing the manufacture of sipuleucel-T to be performed at the same scale, using the same procedures, controls, and unidirectional flow as previously described in the BLA. Improved adjacencies allow better flow of materials and QC samples, and some support areas have improved HVAC systems. Does the Agency agree that the overall conceptual design and operational flows of the expanded facility are acceptable?

Your overall conceptual design and operational flows of the expanded facility appear to be adequate based on the information submitted.

We note from IND 6933 amendment 264 that your intention is to manufacture clinical product for your new phase II study in the same facility. You have noted that your (b)(4) identity assay is not reliable for product (b)(4) (b)(4) used in the phase II study. We recommend that you do not (b)(4) manufacture both clinical and commercial product in the same facility due to your inability to validate the [redacted] assay for the clinical product. We further recommend that if you do wish to manufacture clinical and commercial product in the New Jersey facility that a dedicated module(s) be designed into the expansion plan to maximize segregation.

Discussion: Dendreon responded that they planned to only produce the commercial product once it is licensed, and they would consult with FDA if that plan were to change. FDA stated that Dendreon would need to revalidate the expanded facility. Dendreon agreed.

FDA Response:

2. The manufacturing procedures in the added modules will duplicate the validated process in an equivalent environment. All necessary equipment qualification and validation, as well as aseptic processing validation, will be conducted for the added facilities. Therefore, Dendreon does not intend to repeat the sipuleucel-T manufacturing process validation studies. (Refer to BLA Section 3.2.S.2.5 subsection 2.0.) Does the Agency agree?

FDA Response:

Based on the information submitted in the pre-read package, we agree with your proposal for not repeating the sipuleucel-T manufacturing process validation studies provided that all necessary qualification/validation studies for the expanded facility and equipment including environmental monitoring (EM), as well as aseptic processing validations (APV) are adequately performed.

Please be reminded that the APV should cover the worst-case scenario such as the maximum throughput, occupancy and EM.

Responses to Complete Response Letter

3. Dendreon has submitted complete responses to items 1 through 7 of the May 8, 2007 Complete Response Letter for BLA STN 125197/0. (Refer to BLA Amendment 017 and BLA Amendment 024.) FDA has previously agreed that responses to Items 2, 5, and 6 are sufficient. Does the Agency agree that the responses to Items 1, 3, 4, and 7 are sufficient?

FDA Response:

We note that you have completed the full capacity (WS) qualification study in Modules (b)(4) at your Morris Plains, NJ facility (BLA STN 125197/024). The results appear to be adequate based on the information submitted. This study has addressed the observation Item #1 listed on the Form FDA 483 dated February 16, 2007.

Item #1: Modifications made to how samples are handled and tracked in the QC lab have been substantially improved and we now consider this issue to be resolved. We do have two additional comments: 1)We recommend in order to avoid a situation where QC testing might become rushed in situations where the shelf life of the APH or final product is close to expirations that a minimum time for testing before expiration be established and included in your SOPs. 2) It is unclear if there is a maximum amount of time a test sample can sit in the QC lab before being analyzed. We recommend you validate the stability of test samples for the maximum amount of time they may sit before QC testing is complete. The concern is that you might get inaccurate test results from some samples if they sat for extended periods in the QC lab while other samples were being processed. Our understanding is that final product QC testing could be initiated at any time during the 18 hour final product shelf life.

Discussion: Dendreon responded that they track everything and monitor times and they had data on the stability of each type of test sample.

Item #2 - Stability of (b)(4) product. The information provided in amendment 17 provided appears to be acceptable. We strongly encourage further (b)(4) and final product stability testing as part of your continued product development efforts.

Item #3 - Maintenance of appropriate shipping temperature: the Temperature Map Shipping Study you have proposed appears to be well designed. Please provide results from those experiments when completed.

Item #4 – Packaging time: We appreciate your establishment of process step times. However, final determination on this issue is dependent upon the results from your ongoing final product stability study. Please provide those results when available.

- Data on product shipped from NJ facility: The data provided in amendments 15 and 16 is still under review.

Item #5 - Manufacturing site comparability: We agree that the data support the comparability of product at different manufacturing sites. Your response to this issue is acceptable.

Item #6 - (b)(4) validation. Thank you for providing the information requested to items a, b, and c, including your examination of additional environmental isolates. Our evaluation of this information together with information provided in the BLA is still ongoing with regards to equivalency of the (b)(4) to the CFR method.

Discussion: Dendreon responded that they performed an equivalency study which they would provide in an amendment.

Item #7 - a) Assay validation for b(4) endotoxin – Your response appears to be acceptable.

b) Gram stain – The revalidation of this assay appears to be acceptable.

c) study- The revalidation of this assay appears to be acceptable.

Chronology
Meeting Minutes Drafted/Tull: 1/15/09
Meeting Minutes Finalized/Tull: 2/13/09